INTRODUCTION

The role of mast cells in atopic disease has been well characterized, involving exposure to an allergen, activation via cross-linking cell surface IgE, and release of pro-inflammatory mediators (e.g., IL-6, IL-8, VEGF). Recent evidence has shown, however, that mast cells may be critical players in several inflammatory but non-atopic diseases, instead undergoing IgE-independent activation with selective release of mediators1. Despite this broader implication of mast cells in inflammatory disease, their potential role in inflammatory disorders of the larynx is poorly described. While laryngeal allergy has been described previously2, to our knowledge only one previous study has demonstrated and quantified mast cell presence in the human supraglottis, though not in symptomatic patients3. Here, we identify a subset of patients with redundant, inflamed supraglottic mucosa of unclear etiology, all requiring tracheostomy, and demonstrate the histologic presence of mast cells and clinical response to Cromolyn sodium, an established mast cell stabilizer.

METHODS

Twelve patients underwent supraglottic biopsy and peripheral blood measurement of high sensitivity CRP (hsCRP) during initial workup of their obstructive edema. All 12 patients had previously or at the time of biopsy required a tracheostomy for airway management, illustrating the severity of their laryngeal inflammation. The patients also underwent treatment with Cromolyn sodium for 6-12 weeks. Pre- and post-treatment endoscopic photographs were obtained.

Mast cell counts were determined via c-kit (CD-117) immunohistochemistry staining during routine pathologic analysis. Immunostained slides of tissue were photographed and uploaded into the Vanderbilt University Medical Center Digital Histology Shared Resource Hub via the Leica SCN400 Slide Scanner™ (Leica Biosystems Inc, Buffalo Grove, IL). Slides were imaged at 20x magnification to a resolution of 0.5 um/pixel. 22 patients with supraglottic biopsies were eligible for analysis. Differences in cell counts were statistically analyzed by Student’s t-Test.

RESULTS

The 12 affected patients demonstrated mast cell concentrations in supraglottic tissue biopsies obtained during workup of their obstructive edema of 604 mean cells per high powered field (HPF). This was not significantly different from the control group with 496 mean cells per HPF (p = 0.49). Representative images for both groups of c-kit stained mucosa are shown in Figure 1 and graphically in Figure 2.

Clinically, affected patients showed concomitant elevation of systemic inflammatory markers (mean high sensitivity CRP: 24.9 mg/L, +/- 16.2 mg/L). Interestingly, 8 of 12 patients showed objective improvement with use of inhaled Cromolyn sodium. Seven were able to be decannulated. Endoscopic images illustrate this improvement in two such patients seen in Figure 3.

DISCUSSION

While the existence of laryngeal atopic disease has previously been described4, the role and function of laryngeal mast cells has not. Interestingly, both tissue from our experimental subjects with idiopathic inflammatory disease and the control subjects, obtained from laryngeal carcinoma patients, showed similar levels of mast cell tissue density. Both of these data are consistent with other reported mast cell counts taken from laryngeal carcinoma patients5. Whether this suggests the presence of mast cells in laryngeal mucosa is elevated in both inflammatory and neoplastic disease secondary to an unknown mechanism or, instead, that the larynx is an active host-pathogen interface that harbors mast cells as part of its normal function, is unclear. A future area of study includes examination of healthy laryngeal mucosa (e.g., autopsy specimens) to obtain a ‘true normal’ of resident laryngeal mast cells. Nonetheless, our patients did show evidence of an active mast-cell process as the majority (eight of 12) of the inflammatory patients showed improvement with administration of well-established mast cell stabilizer, Cromolyn sodium. Seven of those patients improved to the point of decannulation. This may suggest that while the number of mast cells in these patients’ laryngeal mucosa do not differ from the control group, they may indeed be more active (i.e., degranulating) as suggested by the clinical improvement from topical therapy.

SUMMARY

1. Mast cells may play a pathogenic role in a subset of patients with inflammatory upper airway disease, even in patients without other atopic symptoms or diseases.

2. Cromolyn sodium therapy may be helpful in treating patients with refractory laryngeal (supraglottic) edema.

3. Further study is needed to delineate the presence and role of mast cells in the normal (healthy) human larynx.

KEY REFERENCES

